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# Synthesis of a novel diarylheptanoid isolated from *Zingiber officinale*

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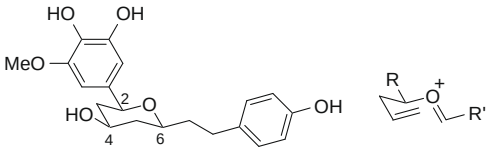
ABSTRACT

Syntheses of 4-acetoxy-2,6-disubstituted tetrahydropyrans via Prins cyclisation of homoallylic alcohols with benzylic aldehydes are described and the methodology is applied in the total synthesis of diarylheptanoid **1** confirming both the structure and absolute configuration of the natural product.



In a programme aimed at the discovery of novel compounds from the Zingiberaceae species, the groups of Cheng and Zhao reported the isolation of a new diarylheptanoid **1** from the methanol extracts of *Zingiber officinale* collected in Yunnan Province, China.[1] Whilst **1** showed no cytotoxicity against a human carcinoma cell line or rat liver hepatocytes, it possessed potent antioxidant properties. The structure of the diarylheptanoid with three equatorial substituents adorning a tetrahydropyran ring, was elucidated through extensive spectroscopic studies. Whilst the (2*S*,4*R*,6*S*) absolute stereochemistry is indicated in the structure of **1**, and an optical rotation of $[\alpha]_D$ −32.5 (*c* 0.75 MeOH) was recorded, the authors make no mention of the absolute configuration.




**1**




**2**

Prins cyclisations are of value for the stereoselective synthesis of tetrahydropyrans and have been used to good effect in natural product synthesis.[2] Using aldehydes and homoallylic alcohols as precursors for the in situ generation of an unsaturated oxocarbenium ion **2** required for the cyclisation, two disconnections of diarylheptanoid **1** may be proposed (Scheme 1).

One approach would involve reaction of a benzylic homoallylic alcohol **A** with aldehyde **B**. Choice of protecting groups for the aromatic alcohols is important as it has been shown that during Prins cyclisations of benzylic alcohols adjacent to an electron-rich aromatic ring, solvolysis and oxonia-Cope rearrangements may occur leading to racemisation and formation of a number of side products.[3] The alternative disconnection gives homoallylic alcohol **D** and protected trihydroxybenzaldehyde **C** as the electrophile. A model study on the synthesis of racemic 4-acetoxytetrahydropyran **4** was undertaken to compare the two potential routes (Scheme 2). Treatment of homoallylic alcohol **3** with dihydrocinnamaldehyde and $BF_3{\cdot}OEt_2$ for 4 h at room temperature, with AcOH as the nucleophile and TMSOAc as a fluoride trap in cyclohexane gave a mixture of products including the required tetrahydropyran **4** (42% yield) and the symmetrical products **5** and **6** arising from oxonia-Cope/allyl transfer processes.

Reaction of alcohol **7** with 4-acetoxybenzaldehyde **8** under identical conditions was found to be slow with significant quantities of starting materials being recovered after 4 h (Scheme 2). However tetrahydropyran **4** was isolated as the sole heterocyclic product. Interestingly, Rychnovsky[4] has shown that symmetrical products **11** and **12** are formed in the $BF_3{\cdot}OEt_2$-promoted reaction of (*S*)-1-phenylbut-3-en-1-ol **9** (87% ee) with dihydrocinnamaldehyde; the major product was the unsymmetrical 4-acetoxytetrahydropyran **10** which was formed with some loss of enantiopurity (68% ee) occurring during the cyclisation (Scheme 3).

Not only do the electronic properties of homoallylic alcohols and aldehydes affect the reaction outcome, but also the conditions, including acid used, solvent, temperature and the nucleophile employed, play an important role.[5] For example, Rychnovsky reported that reaction of benzylic alcohol **9** with dihydrocinnamaldehyde and $SnBr_4$ gave 4-bromotetrahydropyran **13** in 77% yield along with a small amount (8%) of symmetrical product **14**. The contrasting results shown in Scheme 3 were attributed to the Prins cyclisation being much faster with $SnBr_4$ than with $BF_3{\cdot}OEt_2$/AcOH/TMSOAc and so suppressing the competing oxonia-Cope rearrangement.[4] Thus, based on our model study and literature precedent,[3–5] the preferred pathway to our target diarylheptanoid **1** involved reaction of a functionalised benzaldehyde **C** and homoallylic alcohol **D** (Scheme 1).

Further model studies were undertaken to establish appropriate conditions to introduce an oxygen nucleophile at C-4 of the target trisubstituted tetrahydropyran. Trifluoroacetic acid has been used in Prins cyclisations for the efficient synthesis of 4-hydroxy-

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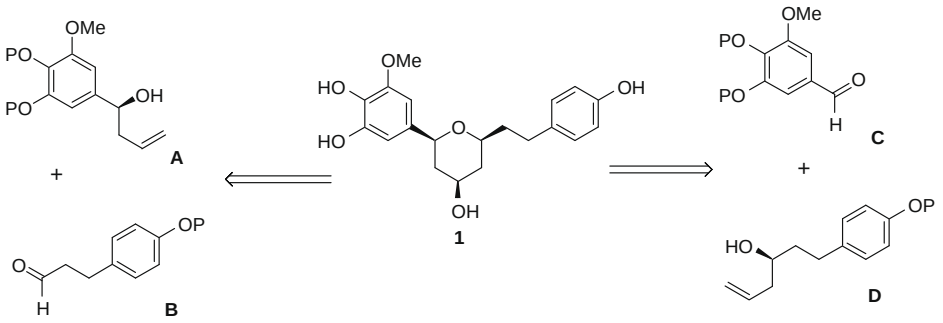
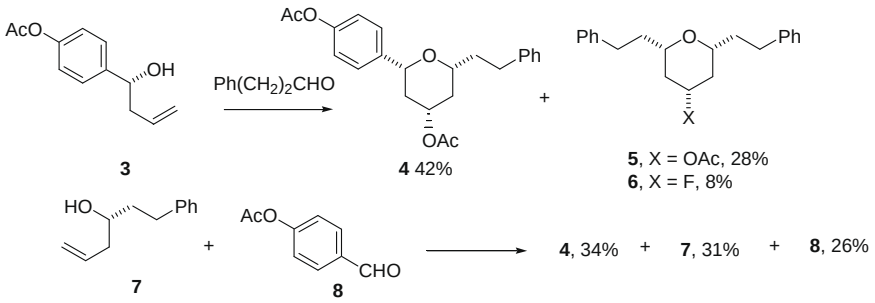
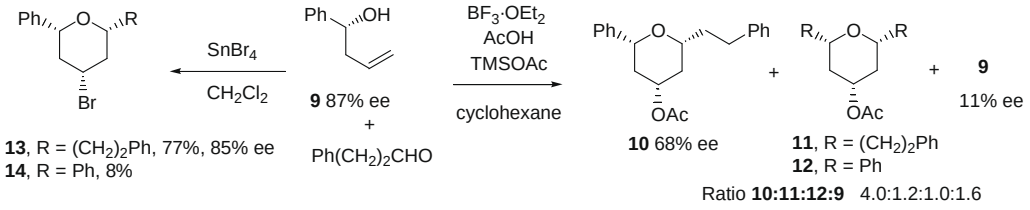



**Scheme 1.** Retrosynthetic analysis of diarylheptanoid **1**.




**Scheme 2.** Model cyclisation studies.




**Scheme 3.** Prins cyclisations with homoallylic alcohol **9**.[4]

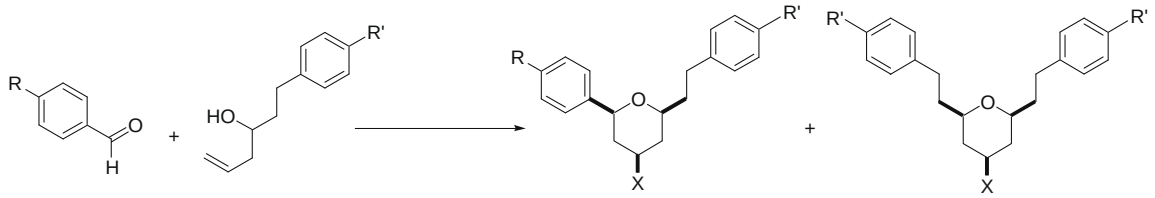
2,3,6-trisubstituted[6] and 4-hydroxy-2,6-disubstituted tetrahydropyrans.[7] In this case, however, treatment of 4-acetoxybenzaldehyde **8** and homoallylic alcohol **7** with TFA in $CH_2Cl_2$, and subsequent base hydrolysis of the resultant ester, gave the required unsymmetrical 2,4,6-trisubstituted tetrahydropyran **15** in only 34% yield accompanied by the symmetrical product **16** (31% yield) and 4-hydroxybenzaldehyde (31% yield) arising from oxonia-Cope rearrangement/allyl transfer processes (Scheme 4). Similarly reaction of homoallylic alcohol **18** and benzaldehyde gave the two tetrahydropyrans **19** and **20** in approximately 1:1 ratio.

Next the $BF_3{\cdot}OEt_2$-mediated reactions of homoallylic alcohol **18** with either 4-acetoxybenzaldehyde **8** or benzaldehyde **17** were investigated using $CH_2Cl_2$ as the solvent and were found to be faster than in cyclohexane. After 4 h at room temperature, acetates **21** and **23** were isolated in good yields (68% and 70%, respectively), accompanied by tetrahydropyrans **22** and **24** arising from attack of fluoride at C-4. No symmetrical products were detected.

Having established suitable conditions for the key Prins cyclisation, this methodology was applied to the total synthesis of the target diarylheptanoid (Scheme 5). Aldehyde **26**, prepared by acetylation of commercially available diol **25**, and homoallylic alcohol **18** were treated under the $BF_3{\cdot}OEt_2$-mediated conditions in $CH_2Cl_2$. The required 4-acetoxytetrahydropyran **27** was isolated in 65% yield, accompanied by 4-fluorotetrahydropyran **28** (15%). Hydrogenolysis of the benzyl ether-protecting group of **27** gave alcohol **29** in 99% yield.

Hydrolysis of the acetate-protecting groups of **29** would give diarylheptanoid **1** in racemic form. However, there was potential to shorten the synthetic route by using a single deprotection step if the phenol of the homoallylic alcohol was protected as an acetate, rather than a benzyl ether. Thus (*S*)-homoallylic alcohol **34** was synthesised from commercially available 3-(4-hydroxyphenyl)propionic acid **30** via aldehyde **32** as shown in Scheme 6. Firstly, alcohol **30** was acetylated to give **31** prior to selective reduction of the carboxylic acid using borane–THF complex. Swern oxidation of the resultant primary alcohol gave aldehyde **32**. (*S*)-Homoallylic alcohol **34** was prepared in 53% yield and 91% ee by treatment of aldehyde **32** with Loh's chiral allyl transfer reagent **33**.[8] Mosher's method[9] was used to confirm the (*S*)-configuration of the novel homoallylic alcohol **34**.

Prins cyclisation of homoallylic alcohol **34** and aldehyde **26** gave the required tetrahydropyran **35** in 81% yield and the 4-fluoro derivative **36** (16%). From the coupling constants in the $^1H$ NMR spectrum of **35** it was evident that all three substituents were in an equatorial orientation.[10] Chiral HPLC analysis of both **35** and **36** revealed an 85% ee, indicating a small loss of enantiopurity dur-



Reaction Conditions: i, TFA, $CH_2Cl_2$, 4 h, rt; ii, $K_2CO_3$, MeOH

**8**, R = OAc **7** R' = H **15**, R = OH, R' = H, X = OH 34% **16**, R' = H, X = OH 31%

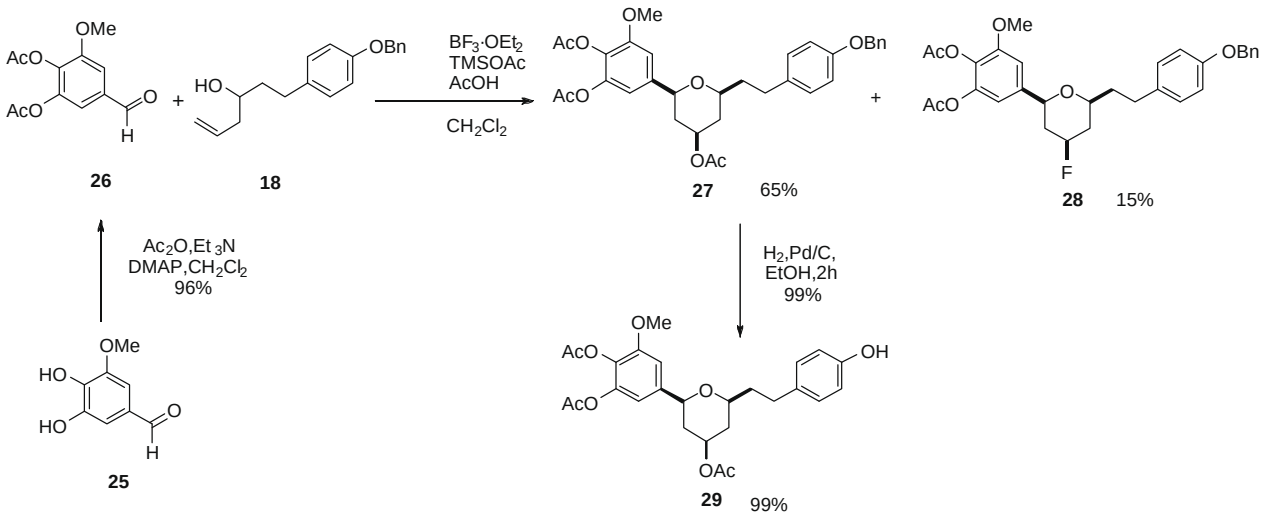
**17**, R = H **18** R' = OBn **19**, R = H, R' = OBn, X = OH, 50% **20**, R' = OBn, X = OH 48%

Reaction Conditions: $BF_3{\cdot}OEt_2$, AcOH, TMSOAc, $CH_2Cl_2$, 4 h, rt

**8**, R = OAc **18**, R' = OBn **21**, R = X = OAc, R' = OBn, 68%
**22**, R = OAc, R' = OBn, X = F, 14%

**17**, R = H **18**, R' = OBn **23**, R = H, R' = OBn, X = OAc 70%
**24**, R = H, R' = OBn, X = F, 20%

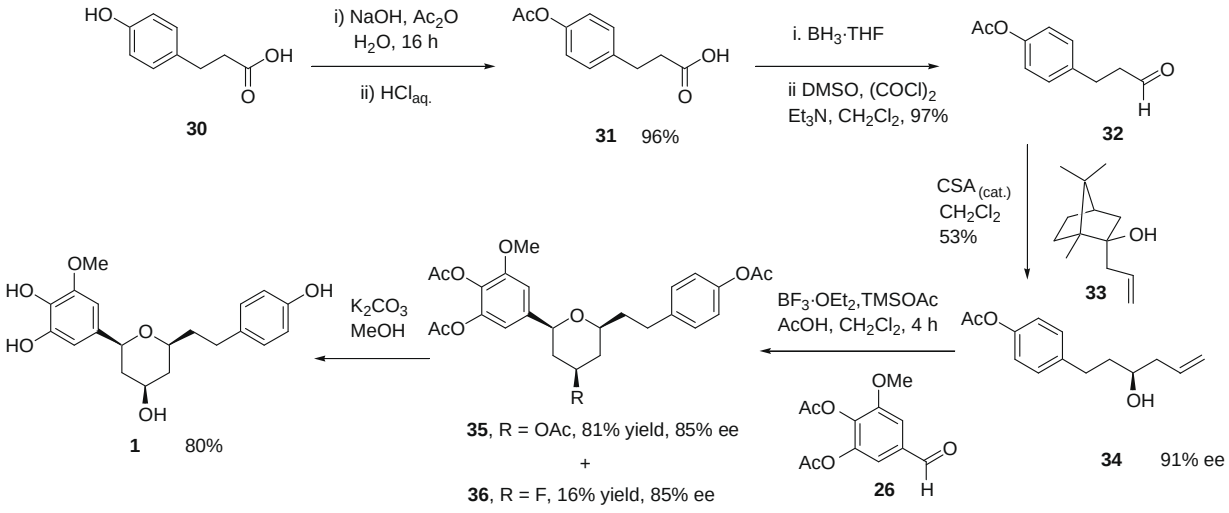
**Scheme 4.** Prins cyclisations.




**26** **18** **27** 65% **28** 15%

**25** **29** 99%

**Scheme 5.** Synthesis of tetrahydropyran **29**.




**30** **31** 96% **32** **33**

**35**, R = OAc, 81% yield, 85% ee

+

**36**, R = F, 16% yield, 85% ee

**1** 80% **34** 91% ee **26**

**Scheme 6.** Synthesis of diarylheptanoid **1**.

ing the cyclisation step. Hydrolysis of the four acetate groups of **35** using potassium carbonate in methanol gave diarylheptanoid **1** in 80% yield. The spectroscopic data for the synthetic sample of **1** and the natural product[1] were identical. Synthetic **1** gave an optical rotation of $[\alpha]_D$ −22 (*c* 1.0 MeOH) which, taking into account the 85% ee, is in accord with the value of $[\alpha]_D$ −32.5 (*c* 0.75 MeOH) reported for the natural product and hence the absolute configuration is confirmed to be (2*S*,4*R*,6*S*).[1]

In conclusion, conditions for the preparation of 4-hydroxy- and 4-acetoxy-2,6-disubstituted tetrahydropyrans via Prins cyclisation of homoallylic alcohols with benzylic aldehydes have been investigated. It was established that use of $BF_3{\cdot}OEt_2$, AcOH and TMSOAc in $CH_2Cl_2$ gave unsymmetrical 4-acetoxytetrahydropyrans in good yields. Interestingly, under these conditions, significant amounts (14–20% yield) of the corresponding 4-fluorides were isolated whereas in previous studies using cyclohexane as the solvent[3,4] either less amounts (or none) of the 4-fluorotetrahydropyrans were isolated and we are currently investigating this further. The first enantioselective total synthesis of diarylheptanoid **1** has been completed confirming the reported structure and absolute stereochemistry.

## Acknowledgement

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10. *Experimental procedure for the Prins cyclisation to* **35** *and* **36**: A stirred solution of aldehyde **26** (0.27 g, 1.07 mmol), homoallylic alcohol **34** (0.25 g, 1.07 mmol), TMSOAc (0.80 mL, 5.35 mmol) and AcOH (0.43 mL, 7.49 mmol) in dry $CH_2Cl_2$ (15 mL) was cooled to 0 °C and treated dropwise with $BF_3{\cdot}OEt_2$ (0.27 mL, 2.13 mmol) under an atmosphere of nitrogen. After stirring at 0 °C for 0.5 h the mixture was allowed to warm to room temperature and was stirred for a further 3.5 h before the addition of $NaHCO_3$ solution (30 mL satd aq) and $CH_2Cl_2$ (15 mL). The layers were separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil (0.66 g). The crude product was purified by flash chromatography eluting with 35% EtOAc/petrol to give 4-acetoxytetrahydropyran **35** as a colourless oil (0.46 g, 81%) and 7-fluorotetrahydropyran **36** as a colourless oil (0.085 g, 16%).
Compound **35**: $R_f$ = 0.15 (35% EtOAc/petrol); $[\alpha]_D$ −20 (*c* 1.0, $CHCl_3$); chiral HPLC (Chiralcel OD-H, 50-80% IPA/hexane over 80 min, 0.25 mL/min), 48.0 min (major), 70.3 min (minor); $\nu_{max}$ (neat)/cm$^{-1}$ 3021 (CH), 2939 (CH), 2857 (CH), 1768 (C=O), 1741 (C=O), 1716 (C=O), 1613 (C=C), 1506, 1368, 1184, 1090, 1011, 908, 751, 730; $\delta_H$ (400 MHz, $CDCl_3$) 1.41 (1H, dt, *J* 12.2, 11.1 Hz, 3-$H_{ax}$), 1.51 (1H, dt, *J* 12.2, 11.1 Hz, 5-$H_{ax}$), 1.80 (1H, dddd, *J* 13.7, 9.4, 7.3, 4.2 Hz, 1′-*H*H), 1.98 (1H, dddd, *J* 13.7, 9.2, 8.2, 5.1 Hz, 1′-H*H*), 2.02 (1H, m, 3-$H_{eq}$), 2.04 (3H, s, –OAc), 2.26 (1H, m, 5-$H_{eq}$), 2.27 (3H, s, –OAc), 2.28 (3H, s, –OAc), 2.29 (3H, s, –OAc), 2.71 (1H, ddd, *J* 14.1, 9.2, 7.3 Hz, 2′-*H*H), 2.81 (1H, ddd, *J* 14.1, 9.4, 5.1 Hz, 2′-H*H*), 3.51 (1H, dddd, *J* 11.1, 8.2, 4.2, 1.8 Hz, 2-H), 3.84 (3H, s, –OMe), 4.38 (1H, dd, *J* 11.1, 2.0 Hz, 6-H), 5.00 (1H, app. tt, *J* 11.1, 4.6 Hz, 4-H), 6.80 (1H, d, *J* 1.9 Hz, 2‴-H or 6‴-H), 6.87 (1H, d, *J* 1.9 Hz, 2‴-H or 6‴-H), 6.98 (2H, m, 3″H), 7.17 (2H, m, 2″H); $\delta_C$ (100 MHz, $CDCl_3$) [20.4, 20.7, 21.2, 21.3 (4 × –OOC*C*$H_3$)], 31.1 (C-2′), 37.0 (C-3), 37.5 (C-1′), 39.2 (C-5), 56.3 (–OMe), 70.4 (C-4), 74.7 (C-2), 76.4 (C-6), [107.3, 112.4 (C-2‴ and C-6‴)], 121.5 (C-3″), 129.4 (C-2″), [131.6, 139.5, 140.6, 143.2, 148.9, 152.3 (C-Ar)], [168.0, 168.3, 169.7, 170.6 (4 × –O*C*OCH$_3$)]; found (ESI) 551.1883 [MNa]$^+$, ($C_{28}H_{32}O_{10}Na$ requires 551.1888).
Compound **36**: $R_f$ = 0.21 (35% EtOAc/petrol);); $[\alpha]_D$ −46 (*c* 1.0, $CHCl_3$); Chiral HPLC (Chiralcel OD-H, 50–80% IPA/hexane over 80 min, 0.25 mL/min), 43.7 min (major), 61.0 min (minor); $\nu_{max}$ (neat)/cm$^{-1}$ 3022 (CH), 2933 (CH), 2857 (CH), 1766 (C=O), 1613 (C=C), 1506, 1368, 1183, 1090, 1008, 750; $\delta_H$ (400 MHz, $CDCl_3$) 1.52 (1H, app. quint., $^3J_{HF}$ 11.2, $J_{HH}$ 11.2 Hz, 3-$H_{ax}$), 1.65 (1H, app. quint., $^3J_{HF}$ 11.2, $J_{HH}$ 11.2 Hz, 5-$H_{ax}$), 1.83 (1H, dddd, *J* 13.7, 9.1, 7.7, 4.2 Hz, 1′-*H*H), 2.00 (1H, dtd, *J* 13.7, 8.6, 5.4 Hz, 1′-H*H*), 2.14 (1H, m, 3-$H_{eq}$), 2.28 (3H, s, –OAc), 2.29 (3H, s, –OAc), 2.30 (3H, s, –OAc), 2.37 (1H, m, 5-$H_{eq}$), 2.73 (1H, ddd, *J* 14.1, 8.6, 7.7 Hz, 2′-*H*H), 2.81 (1H, ddd, *J* 14.1, 9.1, 5.4 Hz, 2′-H*H*), 3.43 (1H, dddt, $J_{HH}$ 11.2, 8.6, 4.2, 2.0 Hz, $^4J_{HF}$ 2.0 Hz, 2-H), 3.86 (3H, s, –OMe), 4.30 (1H, dt, $J_{HH}$ 11.2, 2.0 Hz, $^4J_{HF}$ 2.0 Hz, 6-H), 4.78 (1H, dtt, $^2J_{HF}$ 48.9 Hz, $J_{HH}$ 11.1, 4.7 Hz, 4-H), 6.86 (1H, d, *J* 1.8 Hz, 2‴-H or 6‴-H), 6.89 (1H, d, *J* 1.8 Hz, 2‴-H or 6‴-H), 6.99 (2H, m, 3″-H), 7.18 (2H, m, 2″-H); $\delta_C$ (100 MHz, $CDCl_3$) [20.4, 20.8, 21.2, (3 × –OOC*C*$H_3$)], 31.1 (C-2′), 37.4 (d, $^4J_{CF}$ 1.5 Hz, C-1′), 38.3 (d, $^2J_{CF}$ 16.1 Hz, C-3), 40.3 (d, $^2J_{CF}$ 17.7 Hz, C-5), 56.4 (-OMe), 72.4 (d, $^1J_{CF}$ 159.9 Hz, C-4), 74.1 (d, $^3J_{CF}$ 11.5 Hz, C-2), 76.0 (d, $^3J_{CF}$ 12.3 Hz, C-6), [107.4, 112.5 (C-2‴ and C-6‴)], 121.5 (C-3″), 129.5 (C-2″), [131.2, 139.4 (C–Ar)], 140.3 (d, $^4J_{CF}$ 2.2 Hz, C-1‴), [143.3, 148.9, 152.4 (C-Ar)], [168.0, 168.4, 169.8 (3 × –OOCCH$_3$)]; $\delta_F$ (282.8 MHz) −170.6 (br d, $J_{HF}$ 49.0 Hz); found (ESI) 511.1739 [MNa]$^+$, ($C_{26}H_{29}O_8FNa$ requires 511.1739).